REMARKS

Following entry of this amendment, claims 1, 3, 4, 6-14, and 16-29 will be pending in this application. Claims 2, 5, and 15 are canceled herein without prejudice; claims 1, 3, 4, 6, 8, 14, and 16-19 are currently amended; and new claims 20-29 are added. Support for the amendments and new claims can be found throughout the specification and claims as originally filed, e.g., at page 18, line 12, to page 20, line 3. No new matter has been added.

35 USC § 112, first paragraph

Claims 8-13 were rejected for alleged lack of enablement. The Office action states at page 2 that "the specification, while being enabling for bispecific antibodies that bind factors IX and X and treat a bleeding disorder, does not reasonably provide enablement for generic bispecific antibodies that prevent bleeding disorders." Applicants disagree with the rejection. However, claim 8 has been amended to delete reference to "preventing" and to depend from claim 4, solely to further prosecution. This should obviate the rejection.

Claims 5 and 6 were also rejected for alleged lack of enablement. The Office action states at page 4 that:

> [T]he specification, while being enabling for bispecific antibodies which comprise a) full length VH and VL sequences for each specificity (i.e. a total of 4 sequences), b) one full length sequence (VH or VL) for anti-FIX specificity and one full length sequence (VH or VL) for anti-FX specificity, c) the 12 CDR sequences that when interspersed among appropriate framework sequences yield the desired specificities (i.e. 6 for FIX (CDRs 1-3, heavy and light), and 6 for FX) , or d) 6 CDRs for one specificity with a minimum of one full length sequence (VH or VL) for the other specificity, does not reasonably provide enablement for antibodies comprising partial structural information or partial sequence "functionally equivalent thereto" other than that which has been previously specified.

While not acquiescing in this ground for rejection, applicants have canceled claim 5, rendering the rejection moot as to that claim, and have amended claim 6 to depend from claim 4 and to specify a set of three H chain CDRs and three L chain CDRs for each half of the bispecific

antibody. New claims 22-29 also depend from claim 4 and recite in various ways the structure of the claimed bispecific antibodies. New claim 22 specifies the sequence of a variable domain (VH or VL) for each half of the claimed bispecific antibody; new claim 23 requires that the six CDRs for each specificity be from recited lists; new claim 24 limits the six CDRs for the factor IX/IXa specificity and the sequence of a variable domain for the factor X specificity; new claim 25 specifies the sequence of one variable domain for the factor IX/IXa specificity and a set of six CDRs for the factor X specificity; new claim 26 specifies a variable domain sequence for the factor IX/IXa specificity; new claim 27 limits the sequences of the six CDRs for the factor IX/IXa specificity; new claim 28 specifies the sequence of a variable domain for the factor X specificity; new claim 29 specifies the sequence of the six CDRs for the factor X specificity. Using the guidance provided in the specification and the knowledge in the art at the time of filing, one of ordinary skill would have been able to make and use the claimed antibodies without undue experimentation. In fact, several antibodies comprising the claimed variable regions and sets of CDRs were created and tested for factor VIIIa mimetic activity and blood coagulation activity (see Figs. 12 and 13). Factor VIIIa mimetic activity and/or blood coagulation activity was observed for several of the bispecific antibodies tested. Applicants submit that the claims are fully enabled by the specification.

Claims 1-13, 15, 16, and 18 were rejected as allegedly failing to comply with the written description requirement. Claims 2, 5, and 15 are canceled herein without prejudice, solely to further prosecution. With regard to the remaining claims, applicants respectfully traverse the rejection. The standard for compliance with the written description requirement is whether one of ordinary skill would recognize, based on the specification, that applicants were in possession of the invention. Possession of a genus may be demonstrated by description of a sufficient number of species within the genus. Here, the claimed antibodies all share significant structure, in that they are bispecific antibodies that recognize both a proteolytic enzyme and a substrate thereof. Antibodies are well-known in the art, and include common features such as variable

domains and complementarity determining regions. Countless proteolytic enzymes and their substrates were known in the art at the time of filing.

The pathway for blood coagulation/fibrinolysis is well-characterized and includes several proteases with known substrates, including coagulation factors II (thrombin), VII, IX, X, XI, XII, kallikrein, plasmin, tissue plasminogen activator, and urokinase. Several cofactors of these proteases are also known, e.g., tissue factor is a cofactor of factor VIIa, factor V is a cofactor of factor X, and factor VIII is a cofactor of factor IX. Based on the teachings of the specification and the knowledge in the art at the time of filing, one of ordinary skill would recognize that antibodies could be prepared that bind to any one of these proteolytic factors and its respective substrate, and could substitute for a cofactor that enhances proteolysis of the substrate by the proteolytic factor. Examples of enzymes and substrates that may be targeted by bispecific antibodies are discussed in the specification at page 13, line 16, to page 15 line 5, and include protein Z-related protease inhibitor (ZPI) and factor X (cofactor: protein Z (PZ)); thrombin and thrombin activatable fibrinolysis Inhibitor (TAFI) (cofactor: thrombomodulin (TM)); thrombin and protein C (PC) (cofactor: TM/protein S (PS)); factor Xa and prothrombin (cofactor: factor V/Va); complement C1s and complement C2 (cofactor: complement C4b); and complement regulatory factor I and complement C3b (cofactors: complement regulatory factor H, membrane cofactor protein (MCP), and complement receptor 1 (CR1)). As proof of concept, applicants demonstrated that bispecific antibodies that recognize coagulation factors IX and X could substitute for factor VIII activity and accelerate blood coagulation. Although particular bispecific antibodies for the other enzyme/substrate pairs are not disclosed in the present application, based on applicants' disclosure, one of ordinary skill would recognize that applicants were in possession of the genus of bispecific antibodies that recognize a proteolytic enzyme and its substrate (e.g., coagulation/fibrinolysis factors) and functionally substitute for a cofactor that enhances the enzymatic reaction.

Claims 6 and 22-29 recite bispecific antibodies having defined variable domain or CDR sequences. At the time of filing, one of ordinary skill would recognize that given an antibody with a particular specificity, it would be simple to make and identify variant antibodies that

replace one variable domain or substitute all or part of the framework (non-CDR) regions. Therefore, one of ordinary skill would recognize that applicants were in possession of the genera of antibodies having three or six defined CDRs or one defined variable domain (VH or VL) per specificity (i.e., factor IX/IXa or factor X). Applicants have further demonstrated that the portions of the bispecific antibody that recognize each coagulation factor may often be interchanged while retaining factor VIIIa mimetic and/or blood coagulation activity (see Figs. 12 and 13). Based on the teachings of the specification and the knowledge in the art at the time of filing, one of ordinary skill would recognize that applicants were in possession of the claimed genera of bispecific antibodies. Applicants request reconsideration and withdrawal of the rejection for alleged noncompliance with the written description requirement.

35 USC § 112, second paragraph

Claim 15 was rejected as allegedly unclear. Applicants have canceled claim 15, solely to further prosecution. This obviates the rejection.

35 USC § 101

Claim 15 was rejected as allegedly not claiming a proper process as defined by the statute. Applicants have canceled claim 15, solely to further prosecution. This obviates the rejection.

35 USC § 103

Claim 1-4 and 7-13 were rejected as allegedly being unpatentable over Scheiflinger et al., U.S. Patent 7,033,590 ("Scheiflinger") in view of Paulus, U.S. Patent 4,444,878 ("Paulus"). Applicants respectfully traverse the rejection on the ground that no *prima facie* case of obviousness has been made. Additionally, even if a *prima facie* case of obviousness were to have been made, applicants' specification describes surprising results that mandate a finding of nonobviousness.

The Office action states (at pages 12-13) that:

> Scheiflinger et al. disclose antibodies that bind factor IX and increase the procoagulant activity of factor IX (see entire document, particularly the abstract, column 2, and claims 1-22). These antibodies are disclosed as having FVIII cofactor-like activity, and were demonstrated to have this activity even in the presence of anti-FVIII inhibitory antibodies (see column 2 and examples 2-9, particularly example 7). The antibodies of Scheiflinger et al. are disclosed as being bispecific (see particularly lines 30-50 of column 7) and as being useful for treating multiple conditions associated with excessive bleeding, such as factor VIII inhibitor patients (see particularly columns 2 and 9). The antibodies are also disclosed as being present in therapeutic compositions in various physical forms (column 7). Scheiflinger et al. further disclose that blood coagulation is an enzymatic cascade pathway, that factor IX activates factor X, and that the end result of this pathway is the formation of a stable blood clot made of fibrin (see particularly columns 1 and 2). Note that activated factor IX activates factor X, and thus factor X is a substrate of factor IX. These teachings differ from the claimed invention in that the other antigen recognized by the bispecific antibodies of Scheiflinger et al. is not disclosed as being factor X.
>
> Paulus discloses that bispecific antibodies are to be used as scaffolding to bring together enzymes that belong to the same enzymatic pathway to enhance the efficiency of the reaction pathway (see entire document, particularly column 5 and figures 4 and 5).

Applicants note that the antibodies disclosed and tested by Scheiflinger are monospecific antibodies. As acknowledged by the Office, Scheiflinger does not disclose a bispecific antibody that recognizes factor IX and factor X. In fact, although Scheiflinger lists bispecific antibodies as one type of antibody in which the disclosed anti-factor IX antibodies may be included, Scheiflinger does not disclose any particular bispecific antibodies, nor any particular specificity that may be combined with the factor IX specificity to form a useful bispecific antibody, nor any reason one would bother to produce a bispecific antibody having factor IX specificity combined with anything else. Paulus does not remedy the deficiencies of Scheiflinger. Paulus merely discloses that bispecific antibodies may be used that recognize two enzymes that are sequentially acting on the same substrate, i.e., wherein the first enzyme alters a substrate, and then that altered substrate is used as the substrate of the second enzyme (see column 5 and Fig. 5). Paulus does not teach or suggest a bispecific antibody that recognizes an enzyme and the substrate of that

enzyme (much less a proteolytic enzyme and its substrate), as recited in the present claims. Although factors IX and X are both enzymes, they do not act sequentially to alter the same substrate molecule, as disclosed by Paulus. The substrate of factor IX is factor X, and the substrate of factor X is prothrombin, i.e., an entirely unrelated molecule. Paulus' rationale for making a bispecific antibody is therefore irrelevant to the factor IX/factor X situation. Accordingly, it would not have been obvious to one of ordinary skill at the time of the invention to combine the disclosures of Scheiflinger and Paulus to produce the claimed invention. There was neither motivation to do so, nor an expectation of success to be found in the art. Applicants submit that no *prima facie* case of obviousness has been made.

Furthermore, applicants' disclosure describes results that are surprising in view of the disclosures of Scheiflinger and Paulus, and that provide objective evidence of the nonobviousness of the present antibodies. Scheiflinger discloses particular monospecific antibodies that recognize factor IX and that, as monospecific antibodies, are said to be able to substitute for factor VIII activity *in vitro*. In contrast, applicants started with anti-factor IX antibodies that, when tested in their monospecific configuration, have no appreciable ability to substitute for factor VIII activity. (See Figs. 4 and 5.) Applicants found that combining one of these apparently inactive anti-factor IX antibodies with any of several anti-factor X antibodies in a bispecific configuration resulted in a bispecific antibody that was highly active as a factor VIII mimetic (Figs. 4 and 5). Neither Scheiflinger nor Paulus even faintly suggests that combining (a) an essentially inactive anti-factor IX antibody with (b) an anti-factor X antibody in a bispecific antibody configuration would result in a new activity possessed by neither monospecific antibody alone. Furthermore, Scheiflinger's Example 6 shows that the anti-factor IX antibody disclosed therein gave a maximum of about a 10% reduction in coagulation time (see Table 1 at col. 17 and also Fig. 17). In marked contrast, two of applicants' bispecific antibodies were shown to decrease blood coagulation time by about 50% or more (see Fig. 17). These results are clearly superior to those described in Scheiflinger and not predicted by Scheiflinger or Paulus, alone or in combination.

Based on at least the above arguments and surprising results, applicants submit that the present claims are nonobvious over Scheiflinger and Paulus, alone or in combination. Therefore, applicants request reconsideration and withdrawal of the rejection for alleged obviousness.

Claim 16 was rejected as allegedly being unpatentable over Scheiflinger in view of Paulus, as applied to claims 1-4 and 7-13 above, and further in view of Zuk et al., U.S. Patent 4,208,479 ("Zuk"). Claim 18 was rejected as allegedly being unpatentable over Scheiflinger in view of Paulus and Zuk, as applied to claims 1-4, 7-13, and 16 above, and further in view of Lollar et al., U.S. Patent No. 5,744,446 ("Lollar"). Applicants respectfully traverse the rejections. As discussed above, claims 1-4 and 7-13 are patentable in view of Scheiflinger and Paulus. The Office states (at page 14) that Zuk discloses "providing reagents, such as antibodies, in kits." At the same page, the Office states that Lollar discloses "recombinant factor VIII polypeptides." These disclosures do not remedy the deficiencies of the alleged *prima facie* case over Scheiflinger and Zuk, nor do they negate applicants' surprising results. Applicants submit that claims 16 and 18 are nonobvious in view of Scheiflinger, Paulus, Zuk, and Lollar, alone or in any combination. Applicants request reconsideration and withdrawal of the rejections.

CONCLUSION

Applicants respectfully submit that all claims are in condition for allowance, which action is requested. Applicants do not concede any positions of the Office that are not expressly addressed above, nor do applicants concede that there are not other good reasons for patentability of the presented claims or other claims.

This reply is being submitted with a Petition for Extension of Time and the required fee. Please apply any other required charges or credits to Deposit Account No. 06-1050, referencing Attorney Docket No. 14875-0160US1.

Respectfully submitted,

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